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(54) ALCOHOL METABOLISM ENHANCER

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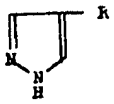
SPECIFICATION

1. TITLE OF THE INVENTION

Alcohol metabolism enhancer

2. SCOPE OF PATENT CLAIMS

1. Alcohol metabolism enhancer having as an active ingredient a 4-alkylpyrazole represented by the general formula



(wherein R represents a C_1 to C_{10} alkyl group).

3. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an alcohol metabolism enhancer for alcohol intolerant persons.

Based on a number or recent studies, it has become known that there are individual differences as well as racial differences in susceptibility to alcohol. For example, according to Science, Vol. 175, p. 449 (1972), alcohol drinking experiments were conducted on Caucasian (white) and Mongoloid (Japanese, Taiwanese, Korean) adults and children without alcohol drinking experience, the results of which revealed that they were divided between a group which exhibited facial flushing after drinking and showed symptoms such as palpitations, tachycardia and dizziness after drinking alcohol, and a group which did not show any particular reaction. Namely, it was found that 70 to 80% of Mongoloids belonged to the former group, while the majority of Caucasians belonged to the latter. The same was true of the children, so it was made clear that the difference in the reaction to alcohol after drinking alcoholic beverages was largely a difference based on race.

Furthermore, there are racial differences in the activity of hepatic alcohol dehydrogenase (hereinafter referred to as ADH), and it has been clarified that this is due to polymorphism of ADH isozymes. In other words, it has been experimentally confirmed that there are low activity isozymes of ADH which generally act at a pH of 10 or higher, and high activity isozymes which act near pH 8 to 9, the former being predominant among whites, such as Europeans and Americans, and the latter being prevalent among the Mongoloid race. Such findings are described for example in

Canadian Journal of Biochemistry, Vol. 43, p. 889 (1965)

Annals of the New York Academy of Sciences, Vol. 151, p. 936 (1968)

European Journal of Biochemistry, Vol. 24, p. 271 (1971);

Japanese Journal of Legal Medicine, Vol. 26, No. 1, p. 46 (1972)

American Journal of Human Genetics, Vol. 27, p. 789 (1975)

Biochemical and Biophysical Research Communications, Vol. 63, p. 202 (1975)

Advances in Enzymology, Vol. 45, p. 450 (1977)

The ADH of Japanese people, as Mongoloids, is examined in detail in these documents.

Furthermore, it is well known that Japanese people are also divided into so-called alcohol intolerant persons, which exhibit facial flushing and discomfort symptoms (also known as drunken sickness) such as tachycardia, palpitations, headache and dizziness, and a normal group, which does not exhibit marked changes after drinking alcohol. The results of measuring blood and breath alcohol and aldehyde levels in the two groups have revealed that in alcohol intolerant persons, after drinking alcohol, for a short period of time aldehyde without exception reaches levels 4 to 6 times higher than in normal persons, while for alcohol, no major difference is found as compared to normal persons. These findings are discussed for instance in

Abstracts of the 10th General Meeting of the Japanese Medical Society of Alcohol Studies, p. 30 (1975)

" 11th " p. 98 (1976)

" 13th " p. 183 (1978)

" 14th " p. 333 (1979)

Japanese Journal of Alcohol Studies, Vol. 14, No. 2, p.101 (1979)

" Vol. 15, No. 1, p. 19 (1980)

" Vol. 15, No. 1, p. 43 (1980)

Disulfirum and cyanamide are aldehyde dehydrogenase inhibitors, which are used for treatment of alcohol intoxication patients, but it is known that when a patient takes these drugs and then drinks alcohol, the patient exhibits a reaction identical to alcohol intolerant persons, i.e., discomfort symptoms (drunken sickness) such as facial flushing, tachycardia, palpitation, headache, dizziness, etc.

Based on all these facts, it can be easily construed that facial flushing and discomfort symptoms (drunken sickness) in alcohol intolerant persons after consuming alcohol is due to the increase of aldehyde accumulation in the organism.

One possible cause of increased aldehyde accumulation in the organism is high ADH activity, as discussed above, but recent findings indicate that this cause is based on genetic differences in aldehyde dehydrogenase (hereinafter referred to as ALDH) (Abstracts of the 15th General Meeting of the Japanese Medical Society of Alcohol Studies, p. 213 and p. 217 (1980)). Namely, ALDH can be of two types, one with a low Km value and one with a high Km value versus substrate, and each type is governed by independent genes. Normally, low-Km ALDH is involved in aldehyde metabolism, but it has been found that nearly 50% of Japanese people lack this enzyme, and while there may be difference in degree, it is clear that these people all exhibit alcohol intolerance symptoms. It has also been made clear that hardly any European or American whites lack this enzyme.

Therefore, the aldehyde accumulation levels in alcohol intolerant persons is mainly governed by the rate of oxidation from alcohol to aldehyde, i.e. by ADH activity, but as discussed above, it is thought that many Japanese people genetically have ADH of high activity, so their aldehyde accumulation levels are high, leading to a high degree of alcohol intolerance.

However, whatever the cause may be, the degree of alcohol intolerance depends on the level of aldehyde accumulation in the organism, and it can be easily surmised that this is determined genetically, and that there is a high proportion of such alcohol-intolerant persons among the Japanese.

It is well known that aldehyde is a substantially more toxic substance that alcohol, and in recent findings, it has been reported that aldehyde inhibits male hormone production with 1000 times the strength of alcohol (*Biochemical and Biophysical Research Communications*, Vol. 94, p. 814 (1980)).

This suggests that increased aldehyde accumulation in the organism during drinking of alcohol, even if temporary, is an undesirable phenomenon.

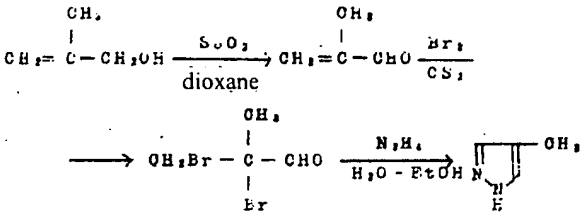
Alcohol is a necessary and indispensable thing in human society, and is indeed properly called "the chief of all medicines" for normal persons, whereas alcohol intolerant persons are unable to enjoy its benefits, and moreover, for the reasons discussed above, alcohol consumption by alcohol intolerant persons leads rather to physiologically undesirable results.

From the viewpoint described above, the present inventors, believing that the development of a method of ameliorating such alcohol metabolism anomalies would bring good news to alcohol intolerant persons, as a result of concerted research efforts, discovered that substances which inhibit ADH activity are suitable for this purpose, and through further research, arrived at the present invention.

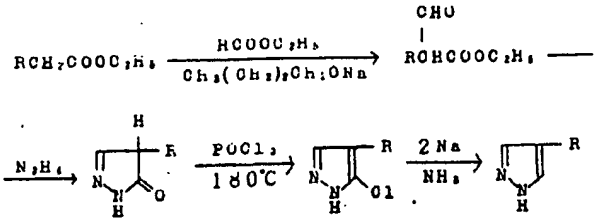
Namely, the present invention is an alcohol metabolism anomaly ameliorating agent for alcohol intolerant persons, having as an active ingredient a 4-alkylpyrazole represented by the general formula

(wherein R represents a C_1 to C_{10} alkyl group).

The compound used in the present invention can be manufactured by publicly known methods. For example, 4-methylpyrazole can be manufactured according to the following chemical reaction formula



by forming a selenic acid of β-methylallyl alcohol, brominating it and then subjecting it to the action of hydrazine. Furthermore, a synthesis method that is common to 4-alkylpyrazoles follows the following chemical formula



(wherein R represents a C_1 through C_{10} alkyl group), wherein alkyl carboxylic acid ethyl ester is subjected to the action of ethyl formate in the presence of sodium butyrate and is formylated and then subjected to the action of hydrazine to obtain 4-alkylpyrazolone-5. The 5-position thereof is chlorinated with phosphorus oxychloride, after which the substance is reduced by subjecting it to the action of metal sodium in liquid ammonia.

The 4-alkylpyrazole manufactured in this manner is known to inhibit ADH activity at low concentrations. For example, the 50% inhibitory concentration (ID_{50}) of 4-methylpyrazole against human ADH activity is 0.04 to 0.10 μg/ml. Furthermore, the toxicity of 4-alkylpyrazole is generally low. For example, the 50% lethal concentration (LD_{50}) when administered orally to rats is 750 to 1000 mg/kg for 4-methylpyrazole, 500 to 750 μg/ml for 4-heptylpyrazole, 750 to 1000 mg/ml for 4-octylpyrazole and 2000 to 2500 mg/kg for 4-decylpyrazole.

These findings are discussed for instance in

Quarterly Journal of Studies on Alcohol, Part A, Vol. 29, No. 2, p. 449 (1968)

Acta Chimica Scandinavica, Vol. 23, p. 255 (1969)

Acta Chimica Scandinavica, Vol. 23, p. 892 (1969)

US Patent No. 2,931,814

The toxicity of 4-methylpyrazole was investigated in more detail, and for example when it was administered orally to rats over a period of 4 weeks at a rate of 200 mg/kg per day, no anomalies were observed. Furthermore, 11.5 mg/kg was administered daily over 38 weeks to investigate primarily the blood, liver and kidney functions, and no anomalies were found.

These findings are discussed in detail in *Experientia*, Vol. 28, p. 1198 (1972) and *Archives of Biochemistry and Biophysics*, Vol. 199, p. 591 (1980).

Because 4-alkylpyrazole is a highly safe substance, as indicated above, there is already experience of administering it to humans. For example, according to *Life Sciences*, Vol. 9, Part II, p. 631 (1970), it has been reported that 4-methylpyrazole was administered orally to humans in the range of 1 to 10 mg/kg, as a result of which ADH was effectively inhibited *in vivo*. Examples of administration to humans are also reported in *Life Sciences*, Vol. 13, p. 113 (1973); *European Journal of Chemical Investigation*, Vol. 7, p. 487 (1977); and *Metabolism*, Vol. 27, p. 631 (1978).

However, there has been no investigation to date of the effects of the administering the present compound to alcohol intolerant persons.

The present inventors discovered that 4-alkylpyrazole, which has strong ADH inhibiting activity and high safety, effectively ameliorates alcohol metabolism anomalies in alcohol intolerant persons.

Conventional administration methods are used as the method of administering the compound used in the present invention. For example, it can be made into tablets by suitably combining with sucrose, lactose or other sugars and calcium carbonate, aluminum hydroxide, calcium stearate, magnesium stearate or other salts, or it can be made into a water-soluble salt and then administered as an aqueous solution. The dosage varies somewhat according to the degree of alcohol intolerance and the amount of alcohol consumption, but normally, 100 to 500 mg (1.5 to 10 mg/kg) in terms of 4-alkylpyrazole is appropriate. Regarding the time of administration, it is preferable to administer 10 to 100 minutes before drinking alcohol.

If the present compound is taken in this manner before drinking alcohol, alcohol intolerant persons who normally present facial flushing and discomfort symptoms (drunken sickness) such as tachycardia, palpitations and headache upon drinking about 50 ml of sake, will not particularly exhibit discomfort symptoms even after drinking 2 to 4 times that amount, allowing them to enjoy drinking just like normal persons.

Next, examples of embodiment will be presented.

Reference example 1

Synthesis of 4-methylpyrazole

28 g of selenium dioxide and 50 ml of dioxane were boiled in a three-neck flask, 27 g of β-methylallyl alcohol was added dropwise thereto, and 16.7 g of a 64 to 74°C distillation fraction (α-methylacrolein) was obtained. This was dissolved in 50 ml of carbon dioxide and dewatered with calcium chloride, after which a carbon disulfide solution of bromine was added dropwise while stirring at 0°C. The reaction was stopped when the color of the bromine had disappeared, and distillation was conducted at ambient pressure to obtain a residue. This was subjected to reduced pressure distillation at 6 mmHg to obtain 29 g of a 73 to 75°C fraction (α, β-dibromo isobutylaldehyde). 16.4 g (71.3 millimol) of α, β-dibromo isobutylaldehyde and 4.89 g (71.5 millimol) of hydrazine hydrochloride were boiled under reflux for 1.5 hours in 100 ml of aqueous ethanol. After concentrating the reaction liquid, the residue was brought to pH 12 with 20% caustic potash and extracted four times with 100 ml ether. The ether extract was washed with water and dewatered with calcium chloride, after which the ether was distilled off and the residue was distilled under reduced pressure at 2 mmHg to obtain 1.3 g of a 78 to 82°C fraction (4-methylpyrazole).

The characteristics of the compound obtained were as follows, confirming it to be 4-methylpyrazole.

1. Appearance:
   Colorless liquid with a sweet aroma.
2. Boiling point
   78 to 81°C (2 mmHg)
3. Silica gel thin layer chromatography
   Rf = 0.61
   Development: water-saturated ethyl acetate
   Detection: presents a salmon pink color when sprayed with 0.5% $Na_2(Fe(ON)_5 \cdot NH_3)$ and then with 10% $NaNO_2$.
4. Nuclear magnetic resonance spectrum ($CDCl_3$ solution)

2.06 ppm	3H (S)	$-CH_3$	
7.26	2H (S)	C3-H, C5-H	
11.74	1H (S)	N-H	

5. ID_{50} against equine ADH activity
   0.12 μg/ml

6. LD_{50} in rats (p.o.)
750 to 1000 mg/kg

Example of embodiment 1

Three healthy adult males (age 30 to 35, 55 kg to 60 kg) known to present facial flushing and exhibit discomfort symptoms such as tachycardia, palpitations and headache upon drinking about 50 ml of sake or 180 ml of beer were selected as subjects, and were orally administered 250 mg 4-methylpyrazole hydrochloride dissolved in 50 ml water and neutralized with sodium bicarbonate after fasting for 6 hours. 15 minutes after the administration, the subjects were given 150 m of sake and were made to drink it over a period of 15 minutes. The results of observing for the degree of facial flushing and investigating for the presence of discomfort symptoms such as a tachycardia, palpitations and headache over a period of two hours following the start of drinking were that all of the subjects hardly exhibited any facial flushing and did not develop the aforementioned discomfort symptoms.

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